

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
13 December 2001 (13.12.2001)

PCT

(10) International Publication Number
WO 01/94318 A2

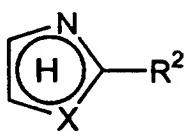
- (51) International Patent Classification⁷: **C07D 233/54**, 277/24, 249/08, 233/90
- (21) International Application Number: PCT/US01/16727
- (22) International Filing Date: 22 May 2001 (22.05.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/209,252 5 June 2000 (05.06.2000) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

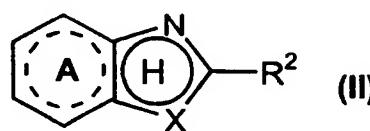
— without international search report and to be republished upon receipt of that report

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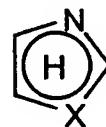
(54) Title: METHOD FOR SYNTHESIS OF SUBSTITUTED AZOLE LIBRARIES



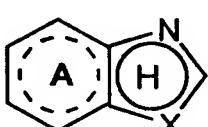
(I)



(II)



(a)



(b)

(57) Abstract: The invention relates to methods of synthesizing libraries of diverse and complex 2-substituted azole compounds of general formula (I) or (II) wherein X, R² and the ring components (a) and (b) are as described herein, novel intermediates useful for synthesizing such substituted azole compounds and methods for identifying and isolating the compounds.

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METHOD FOR SYNTHESIS OF SUBSTITUTED AZOLE LIBRARIES

CROSS REFERENCE TO RELATED APPLICATION

This application claims the priority of US provisional application serial
5 number 60/209,252 filed June 5, 2000, the contents of which are hereby
incorporated by reference.

FIELD OF THE INVENTION

The present invention is directed to a method of synthesizing libraries of
diverse and complex 2-substituted azole derivatives and novel intermediate
10 compounds.

BACKGROUND OF THE INVENTION

Compounds having biological activity can be identified by screening
diverse collections of compounds (i.e., libraries of compounds) produced
15 through synthetic chemical techniques.

The generation of chemical libraries on and off solid resins have proven
to be a valuable resource for the pharmaceutical industry in their endeavors to
discover new drugs using high throughput screening (HTS) techniques. In
20 creating the libraries, the compounds are ideally synthesized *in situ* in solution
phase or on a solid support. However, relatively simple synthetic methods to
produce a diverse collection of such derivatives *in situ* are often not available.

Such screening methods include methods wherein each member of the
25 library is tagged with a unique identifier tag to facilitate identification of
compounds having biological activity or where the library comprises a plurality
of compounds synthesized at specific locations on the surface of a solid
substrate wherein a receptor is appropriately labeled to identify binding to the
compound, e.g., fluorescent or radioactive labels. Correlation of the labeled
30 receptor bound to the substrate with its location on the substrate identifies the

binding compound. Using these techniques, the development of efficient high throughput screening has greatly enhanced the pharmaceutical industry's ability to screen large numbers of compounds for biological activity. Central to these methods is the screening of a multiplicity of compounds in the library and
5 the ability to identify the structures of the compounds that have a requisite biological activity.

Pharmaceutical drug discovery relies heavily on studies of structure-activity relationships wherein the structure of "lead compounds" is typically
10 altered to determine the effect of such alteration on activity. Alteration of the structure of the lead compounds permits evaluation of the effect of the structural alteration on activity.

Thus, libraries of compounds derived from a lead compound can be
15 created by including derivatives of the lead compound and repeating the screening procedures. In this manner, compounds with the best biological profile, i.e., those that are most active and which have the most ideal pharmacologic and pharmacokinetic properties, can be identified from the initial lead compound.
20

Recently, 2-substituted oxazoles were found to be potent as MMP inhibitors (Sheppard, et al, in *Bioorg Med Chem Lett* 8(22), 3251 (1998)); 2-substituted imidazoles were found to produce local anesthetic effects (Colombo, et al., *Rev Farmacol Clin Exp*, 4(1), 41-47 (1987); and 2-substituted
25 thiazoles were found to be selective inhibitors of 5-lipoxygenase (Bird, et al., *5th Int Conf Inflamm Res Assoc* (Sept 23-27 Whit Haven) Abst 85, 1990).

Synthesis of substituted nitrogen containing heteroaryls using solution phase chemistry has been previously described. Khristich et al., in *Khimia Geterotsiklicheskikh Soedineii*, 8, 1136-36 (1983) describe the solution phase synthesis of α -(1-methyl-2-benzimidazolyl)benzyl benzoates. Roe et al., in *JCS* p 2195 (1963) describe the thermal condensation of imidazoles with carbonyl
30

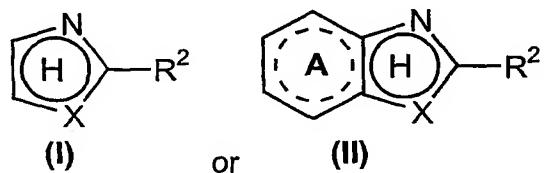
compounds. Papadopolous, in *J. Org. Chem.*, 42 (24) 3925-29, (1977) describes reaction of imidazoles with isocyanates, while Papadopolous et al., in *J. Org. Chem.*, 44(1) 99-104 (1979) describe reactions of azoles with isocyanates. Cleavage of the silicon-carbon bond of 2-trimethylsilyl-1-methylimidazole and 2-trimethylsilyl-1-benzimidazole to yield 2-substituted imidazoles and 2-substituted benzimidazoles is described by Pinkerton, F.H. and Thames, S.F., in *J. Heterocycl. Chem.* 9(1), 67-72 (1972). Dondoni et al., in *J. Org. Chem.*, 53, 1748-61 (1988) describe the synthesis of (trimethylsilyl)thiazoles which are reacted with carbonyl compounds to prepared highly substituted thiazoles.

In order to develop new pharmaceutical drugs to treat various disease conditions, it would be highly desirable to be able to generate such libraries of substituted azole derivatives and novel intermediate compounds. Thus, there is a need for a facile in situ method for the generation of a multiplicity of substituted azole derivatives and novel intermediate compounds.

SUMMARY OF THE INVENTION

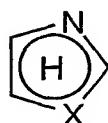
The present invention is directed to a process for assembly of diverse, 2-substituted azole derivatives and novel intermediate compounds using available azoles as starting materials. The rapid synthesis of such highly complex drug-like molecules is unexpected and surprising.

Accordingly, the invention is directed to a method of synthesizing 2-substituted azole derivatives having the formula (I) or (II):



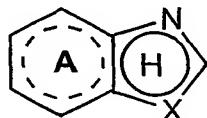
wherein

- . X is selected from the group consisting of NH, NR^A, and S;



represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group consisting of N, O and S;

- 5 provided that the additional heteroatoms are not at the attachment point of the R² group (i.e. the R² group is always attached to a ring carbon);
 provided that the 5 membered ring remains aromatic in nature;
 wherein the 5 membered ring is optionally substituted with one to three substituents independently selected from the group consisting of halogen,
 10 hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocycll, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R, -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocycll may be further optionally substituted with one or more substituent
 15 is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;



represents a 9 membered ring structure, wherein the five membered portion of the ring structure - - is aromatic and the six



- membered portion of the ring structure - - is saturated, partially unsaturated, or aromatic;

- wherein the 5 membered portion of the ring structure is optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocycll, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents

are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

5 wherein the 6-membered portion of the ring structure may further optionally containing one to four additional heteroatoms selected from the group consisting of N, O and S;

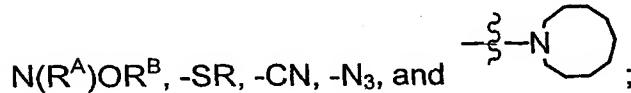
10 wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

15 wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four additional heteroatoms selected from the group consisting of N, O and S;



R² is selected from the group consisting of

Z is selected from the group consisting of hydrogen, -OR^A, -NR^AR^B, -



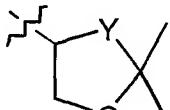
20 wherein

represents a three to eight membered heterocyclyl group bound at the N atom, wherein the heterocyclyl group is saturated, partially unsaturated or aromatic; when the heterocyclyl group is a saturated six to eight membered heterocyclyl, the heterocyclyl group may optionally contains a group selected from O, CHR, NR, S, SO, or SO₂, provided that that the group is separated from the N atom by at least two carbon atoms; and wherein the heterocyclyl group is optionally substituted with one or more substituents independently selected from R;

25

5 R^3 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aralkyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

10 R^4 is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, -COOR, -COR, -CONR^CR^D, -alkyl-COOR,



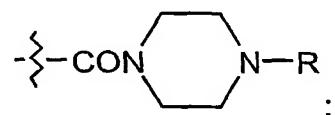
heterocycle and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents

15 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono- or di-substituted amino, cyano or nitro; wherein Y is selected from the group consisting of O, S and NR^A;

20 R^5 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents

25 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

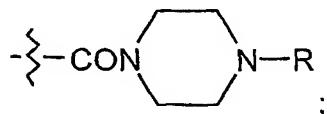
R^6 is selected from the group consisting of hydrogen, alkyl, aralkyl,



cycloalkyl, -COOR, -COR, -SO₂R, -CONR^CR^D and ;

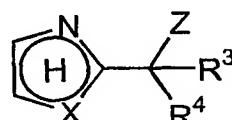
where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and

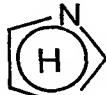
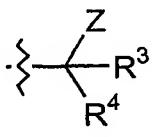


- where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl,
- 5 halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocycl ring structure;
- and pharmaceutically acceptable salt, esters and pro-drugs thereof; by a facile reaction of an azole compound with a carbamyl chloride followed by reaction in situ with an aldehyde or isocyanate to yield the desired
- 10 2-substituted azole.

More particularly, the present invention is directed to a process for preparing compound of the formula (Ia)



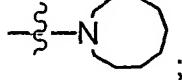
(Ia)

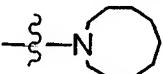
- 15 wherein
- X is selected from the group consisting of NH , NR^A , and S ;
-  represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group consisting of N, O and S;
- 20 provided that the additional heteroatoms are not at the attachment point of the  group;
- provided that the 5 membered ring remains aromatic in nature;
- wherein the 5 membered ring is optionally substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, alkenyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocycl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -
- 25

COR, -SO₂ and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl,

- 5 alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

Z is selected from the group consisting of hydrogen, -OR^A, -NR^AR^B,

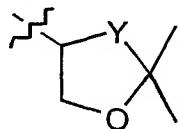
-SR, -N(R^A)OR^B, -CN, -N₃ and ;

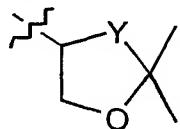
wherein  represents a three to eight membered heterocyclyl group bound at the N atom, wherein the heterocyclyl group is saturated,

- 10 partially unsaturated or aromatic; when the heterocyclyl group is a saturated six to eight membered heterocyclyl, the heterocyclyl group may optionally contains a group selected from O, CHR, NR, S, SO, or SO₂, provided that that the group is separated from the N atom by at least two carbon atoms; and wherein the heterocyclyl group is optionally substituted with one or more substituents
- 15 independently selected from R;

R³ is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aralkyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

20 R⁴ is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, -COOR, -COR, -CONR^CR^D, -alkyl-COOR,



- heterocyclyl and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents
- 25 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono-or di-substituted amino, cyano or nitro; and where Y is selected from the group consisting of O, S and NR^A;

where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

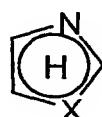
5 where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocycl ring structure;

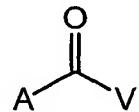
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15 which method comprises reacting a compound of formula (III)



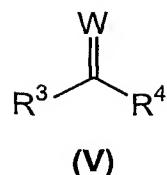
(III)

with a compound of formula (IV)

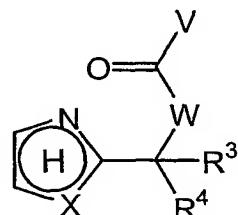


(IV)

20 wherein A is selected from F, Cl, Br, and -OC(O)-t-butyl and wherein V is a sterically hindered group, in a non-protic solvent; and then reacting with a compound of formula (V)



wherein W is selected from the group consisting of -O, - NSO_2R , - NSOR , - NCOR , - NCOOR , - NCONR^CR^D , - NOCOR and - NR , to form the corresponding compound of formula (Ic)



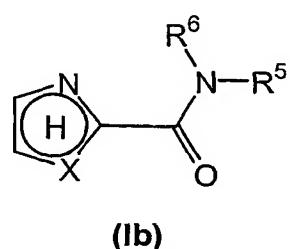
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and optionally reacting the compound of formula (Ic) with a compound of formula (VI)



wherein Z is as previously defined, to yield the corresponding compound 10 of formula (Ia).

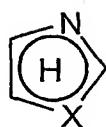
The present invention is further directed to a process for the synthesis of compounds of the formula (Ib)



15

wherein

X is selected from the group consisting of NH, NR^A and S;



represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group consisting of N, O and S;

provided that the additional heteroatoms are not at the attachment point
5 of the -C(O)NR⁵R⁶ group;

provided that the 5 membered ring remains aromatic in nature;
wherein the 5 membered ring is optionally substituted with one to three
10 substituents independently selected from the group consisting of halogen,
hydroxy, alkyl, halogenated alkyl, alkenyl, cycloalkyl, alkoxy, aryl, aralkyl,
heterocycl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -
COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are
independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the
cycloalkyl, aryl or heterocycl may be further optionally substituted with one or
more substituent is independently selected from halogen, hydroxy, alkyl,
15 halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

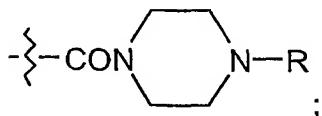
R⁵ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl,
cycloalkyl, fluorinated alkyl and heterocycl; wherein the aryl, aralkyl or
heterocycl may be optionally substituted with one or more substituents
independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy,
20 amino, mono-or di-substituted amino, cyano or nitro;

R⁶ is selected from the group consisting of hydrogen, alkyl, aralkyl,

cycloalkyl, -COOR, -COR, -SO₂R, -CONR^CR^D and ;

where R is selected from the group consisting of alkyl, aryl, aralkyl,
cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the
25 aryl, aralkyl or heterocycle may be optionally substituted with one or more
substituents independently selected from halogen, hydroxy, alkyl, halogenated
alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

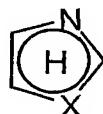
where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



- where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocyclcyl ring structure;
- 5

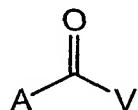
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which method comprises reacting a compound of formula (III)



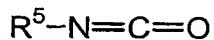
(III)

with a compound of formula (IV)



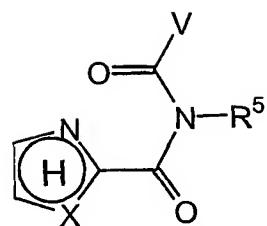
(IV)

- 15 wherein A is selected from F, Cl, Br and -OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent; and then reacting with a compound of formula (VIII)



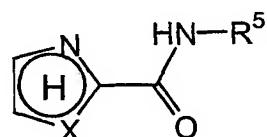
(VIII)

- wherein R^5 is as previously defined, to yield the compound of formula
20 (Id)



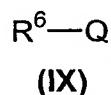
(Id)

reacting the compound of formula (Id) with an inorganic base to yield the compound of formula (Ie)



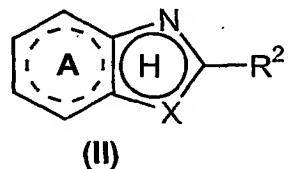
(Ie)

- 5 optionally reacting the compound of formula (Ie) with a compound of formula (IX)

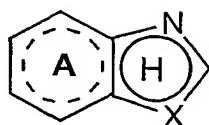


wherein Q is selected from the group consisting of chlorine, bromine and iodine, in the presence of a base, to yield the corresponding compound of
10 formula (Ib).

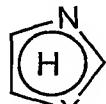
A further aspect of the present invention is the synthesis of compounds of formula (II):



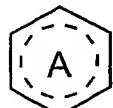
- 15 wherein
X is selected from the group consisting of NH, NR^A and S;



represents a 9 membered ring structure, wherein the five

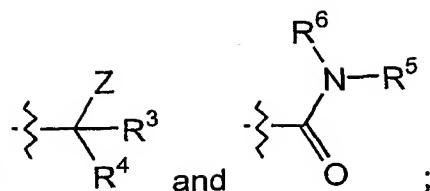


membered portion of the ring structure - - is aromatic and the six



membered portion of the ring structure - - is saturated, partially unsaturated, or aromatic;

- 5 wherein the 5 membered portion of the ring structure is optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents
- 10 are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- wherein the 6-membered portion of the ring structure may further
- 15 optionally containing one to four additional heteroatoms selected from the group consisting of N, O and S;
- wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents
- 20 are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent independently selected from halogen, hydroxy, alkyl,
- halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- 25 halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;



R^2 is selected from the group consisting of

Z is selected from the group consisting of hydrogen, $-OR^A$, $-NR^A R^B$, -

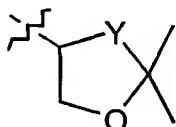
$N(R^A)OR^B$, $-SR$, $-CN$, $-N_3$ and

wherein represents a three to eight membered heterocyclyl

- 5 group bound at the N atom, wherein the heterocyclyl group is saturated, partially unsaturated or aromatic; when the heterocyclyl group is a saturated six to eight membered heterocyclyl, the heterocyclyl group may optionally contain a group selected from O, CHR, NR, S, SO, or SO₂, provided that that the group is separated from the N atom by at least two carbon atoms; and wherein the
10 heterocyclyl group is optionally substituted with one or more substituents independently selected from R;

R^3 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, $-COR$, $-COOR$ and $-CONR^C R^D$; wherein the aralkyl may be optionally substituted with one or more substituents independently
15 selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

R^4 is selected from the group consisting of, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, $-COOR$, $-COR$, $-CONR^C R^D$, $-alkyl-COOR$,



heterocycle and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl or

- 20 heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono- or di-substituted amino, cyano or nitro; wherein Y is selected from the group consisting of O, S and NR^A ;

- R^5 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl,
25 cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents

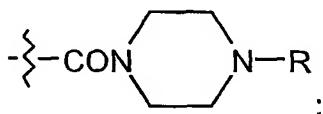
independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

R^6 is selected from the group consisting of hydrogen, alkyl, aralkyl,

cycloalkyl, -COOR, -COR, -SO₂R, -CONR^CR^D and

5 where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

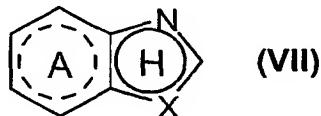
10 where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONRC^BR^D and



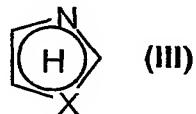
where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle;

15 wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocycl ring structure;

according to either of the processes disclosed herein, with appropriate
20 substitution of a compound of formula (VII)



for the corresponding monocyclic compound of formula (III)



DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "alkyl" whether used alone or as part of a substituent group, shall denote straight and branched chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, 5 t-butyl, pentyl and the like. Unless otherwise noted, "lower" when used with alkyl means a carbon chain composition of 1 to 4 carbon atoms. Similarly, as used herein, the term "alkenyl", whether used alone or as part of a substituent group, shall denote straight and branched chain alkene radicals, i.e. straight or branched chains containing at least one double bond. For example, alkenyl 10 radicals include allyl, vinyl, and the like. Similarly, as used herein, the term "alkynyl", whether used alone or as part of a substituent group, shall denote straight and branched chain alkyne radicals, i.e., straight or branched chains containing at least one triple bond. For example, alkynyl radicals include -CCH, -CH₂CCH (propargyl), -CH₂CCCH₃, and the like.

15

As used herein, unless otherwise noted, "alkoxy" shall denote an oxygen ether radical of the above described straight or branched chain alkyl groups. For example, methoxy, ethoxy, n-propoxy, sec-butoxy, t-butoxy, n-hexyloxy and the like.

20

As used herein, "halogen" shall mean chlorine, bromine, fluorine and iodine.

25 As used herein, unless otherwise noted, "aryl" shall refer to carbocyclic aromatic groups such as phenyl, naphthyl, and the like.

As used herein, unless otherwise noted, "aralkyl" shall mean any lower alkyl group substituted with an aryl group such as phenyl, naphthyl and the like. Suitable examples of aralkyls include benzyl, 1-(phenyl)ethyl, naphthylmethyl, and 30 the like.

As used herein, the term "cycloalkyl" shall denote any monocyclic three to eight membered, saturated carbocyclic ring structure. Suitable examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

- 5 As used herein, unless otherwise noted, the terms "heterocycle", "heterocycl" and "heterocyclo" shall denote any five or six membered monocyclic, nine or ten membered bicyclic or thirteen or fourteen membered tricyclic ring structure containing at least one heteroatom selected from the group consisting of N, O and S, optionally containing one to four additional heteroatoms,
- 10 10 wherein the ring structure is saturated, partially unsaturated, aromatic or partially aromatic. The heterocycl group may be attached at any heteroatom or carbon atom which results in the creation of a stable structure.

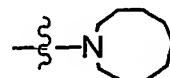
Exemplary monocyclic heterocyclic groups can include pyrrolidinyl,
15 pyrrolyl, indolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, 4-piperidonyl, pyridyl, N-oxo-pyridyl,
20 pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothiopyranyl sulfone, morpholinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, dioxanyl, isothiazolidinyl, triazinyl, triazolyl and the like.

25 Exemplary bicyclic heterocyclic groups include benzothiazolyl, benzoxazolyl, benzothienyl, quinuclidinyl, quinolinyl, quinolinyl-N-oxide, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,1-b]pyridinyl), or
30 furo[2,3-b]pyridinyl, dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), benzothiazolyl, benzisoxazolyl, benzodiazinyl, benzofurazanyl, benzothiopyranyl, benzotriazolyl, benzpyrazolyl,

dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydrobenzopyranyl, indolinyl, isochromanyl, isoindolinyl, naphthyridinyl, phthalazinyl, piperonyl, purinyl, pyridopyridyl, quinazolinyl, tetrahydroquinolinyl, thienofuryl, thienopyridyl, thienothienyl and
5 the like.

Exemplary tricyclic heterocyclic groups include phenoxazinyl, phenazinyl, phenothiazinyl, carbozolyl, perimidinyl, phenanthrolinyl, carbolinyl, naphthothienyl, thianthrenyl, and the like.

10

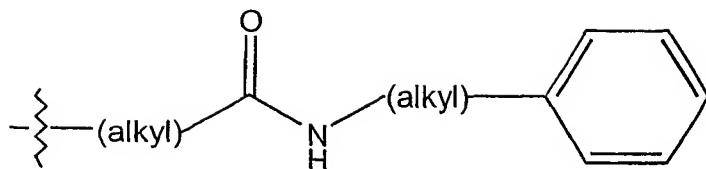


In the definition of Z, suitable examples of the group include pyrazol-1-yl, imidazol-1-yl, pyrrol-1-yl, 1,2,4-triazol-1-yl, 1,2,4-triazol-4-yl, 1,2,3-triazol-1-yl, aziridin-1-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, morpholin-1-yl, 4-methyl-diazepin-1-yl, azepin-1-yl, diazepin-1-yl, 4-methyl-piperazin-1-yl,
15 and the like.

When a particular group is "substituted" (e.g., cycloalkyl, aryl, heterocyclyl, heteroaryl), that group may have one or more substituents, preferably from one to five substituents, more preferably from one to three
20 substituents, most preferably from one to two substituents, independently selected from the list of substituents.

With reference to substituents, the term "independently" means that when more than one of such substituents is possible, such substituents may be
25 the same or different from each other.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a
30 "phenylalkylaminocarbonylalkyl" substituent refers to a group of the formula



The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment,
5 observation or experiment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a
10 researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well
15 as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

For the purposes of this invention, the term "chemical library" means a collection of molecules prepared by the method of the invention based on
20 logical design by means of simultaneous or parallel chemical reactions. Each species of molecule in the library is referred to as a member of the library.

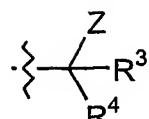
Abbreviations used in the specification, particularly the Schemes and Examples, are as follows:

25

DIPEA	=	Diisopropylethylamine
DMF	=	N,N-Dimethylformamide
Et	=	Ethyl (-CH ₂ CH ₃)
Ex #	=	Example Number

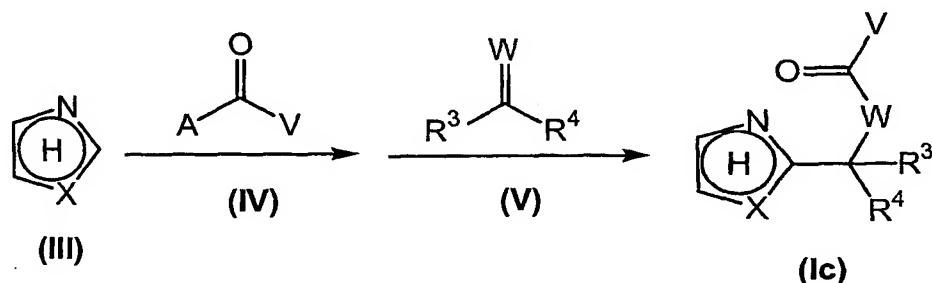
Me	=	Methyl (-CH ₃)
Pd(PPh ₃) ₄	=	Palladium, tetrakis(triphenylphosphine)-
Ph	=	Phenyl (-C ₆ H ₅)
TEA	=	Triethylamine
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran

Compounds of formula (Ia), compounds of formula (I) wherein R² is



may be prepared using solution phase chemistry according to the process outlined in Scheme 1.

5

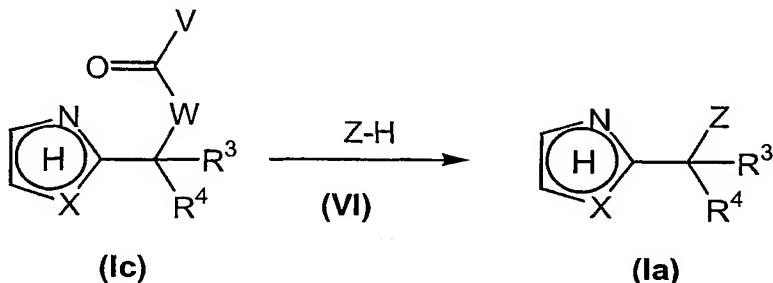


SCHEME 1

- Accordingly, a compound of formula (III), a known compound or
10 compound prepared by known methods, is reacted sequentially with a compound of formula (IV), wherein A is selected from F, Cl, Br or -OC(O)-t-butyl and wherein V is a sterically hindered group such as t-butyl, adamantyl, N(alkyl)₂, N(aryl)₂, 2,6-dimethylphenyl, 2,6-disubstituted phenyl, O-t-butyl, O-isopropyl, O-adamantyl, and the like, at a temperature in the range of about
15 0°C to about reflux in a non-protic solvent such as acetonitrile, dioxane, THF, and the like;
- and then reacted with a compound of formula (V), wherein W is -O, -NSO₂R, -NSOR, -NCOR, -NCOOR, -NCONR^CR^D, -NOCOR or -NR, in the presence of an organic base such as TEA, DIPEA, and the like, to yield the
20 corresponding compound of formula (Ic).

Compounds of formula (Ic) wherein W is O, may be further converted to compounds of formula (Ia), wherein Z is not hydrogen, according to the process outlined in Scheme 2.

5

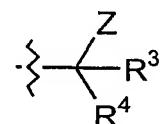


Scheme 2

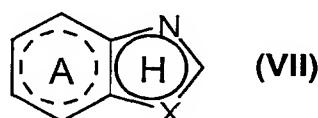
Accordingly, the compound of formula (Ic) is reacted with a compound of formula (VI), in a non-protic solvent such as acetonitrile, dioxane, THF, and the like, in the presence of an acid such as TFA, and the like, at a temperature in the range of about 0°C to about reflux, preferably at about reflux temperature, to form the corresponding compound of formula (Ia).

15 When in the compound of formula (Ia) Z is H, the compound of formula (Ic) is reduced by hydrogenation with a metal catalyst such as palladium, platinum, palladium on carbon, and the like, in an organic solvent such as methanol, ethanol, ethyl acetate, acetic acid, THF, DMF, and the like, to form the corresponding compound of formula (Ia).

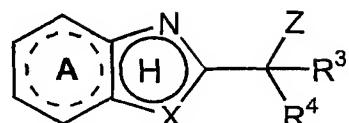
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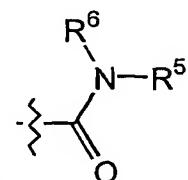
Similarly, compounds of formula (II) wherein R² is R⁴ may be prepared according to the process as outlined in Schemes 1&2, with appropriate substitution of a compound of formula (VII)



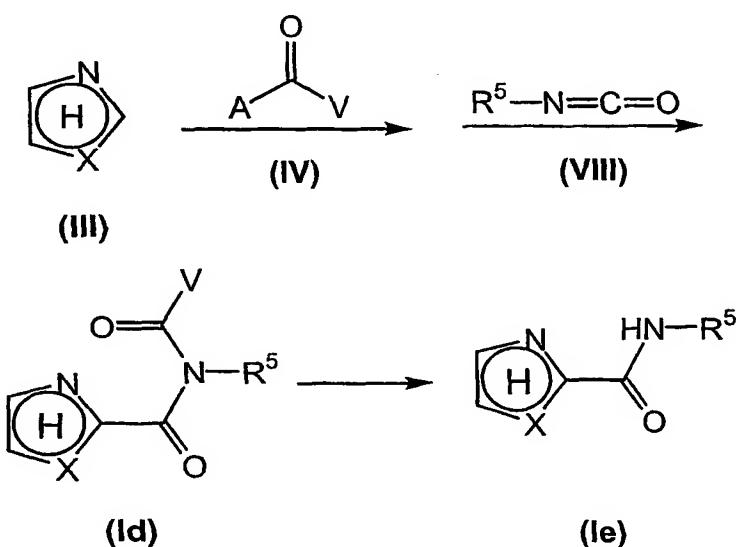
for the compound of formula (III), to yield the corresponding compound of formula (IIa)



(IIa)



- 5 Compounds of formula (I) wherein R² is  may be prepared according to the process outlined in Scheme 3.



10

Scheme 3

More specifically, a compound of formula (III), a known compound or compound prepared by known methods, is reacted sequentially with a compound of formula (IV), wherein A is selected from F, Cl, Br or $-OC(O)-t$ -butyl, and wherein V is a sterically hindered group such as t-butyl, adamantyl, $N(alkyl)_2$, $N(aryl)_2$, 2,6-dimethylphenyl, 2,6-disubstituted phenyl, O-t-butyl, O-isopropyl, O-adamantyl, and the like, at a temperature in the range of about

0°C to about reflux, preferably a about reflux temperature, in a non-protic solvent such as acetonitrile, dioxane, THF, and the like;

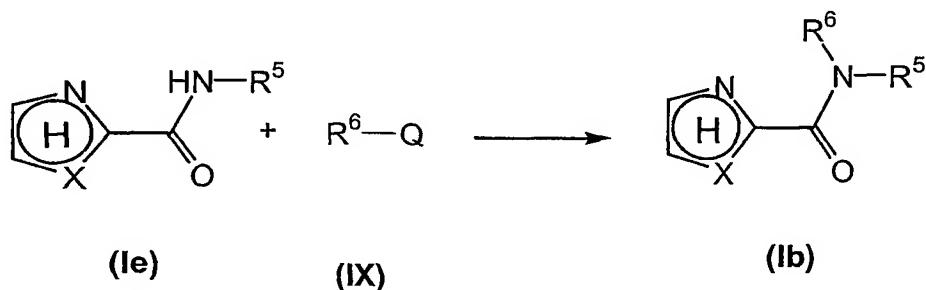
and then reacted with a suitably substituted isocyanate of formula (VIII), in the presence of a base such as TEA, DIPEA, and the like, at a temperature

- 5 in the range of about 0°C to about reflux, preferably at about reflux temperature, to form the corresponding compound of formula (Id).

The compound of formula (Id) is further optionally reacted with an inorganic base such as sodium hydroxide, to form the corresponding

- 10 compound of formula (Ie). Alternatively, the compound of formula (Id) is further optionally reacted with an inorganic base such as potassium carbonate, sodium carbonate, and the like, in the presence of water, to form the corresponding compound of formula (Ie).

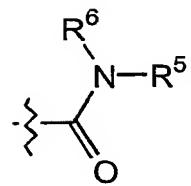
- 15 The compound of formula (1e) is optionally further reacted to form the compound of formula (1b) according to the process outlined in Scheme 4.



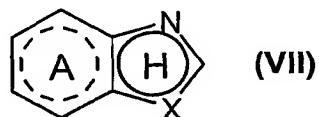
Scheme 4

20

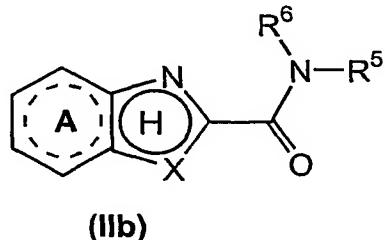
Accordingly, the compound of formula (Ie) is reacted with a compound of formula (IX), wherein Q is selected from the group consisting of chlorine, bromine and iodine, in the presence of a base such as NaH, potassium t-butoxide, potassium carbonate, and the like, to yield the corresponding compound of formula (Ib).



Similarly, compounds of formula (II) wherein R² is prepared using the solution phase chemistry outlined in Scheme 5, with appropriate substitution of a compound of formula (VII)

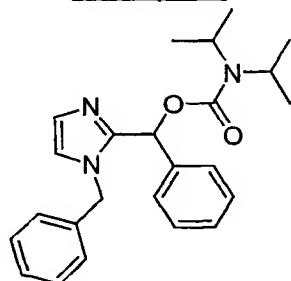


5 for the compound of formula (III), to produce the corresponding compound of formula (IIb).



10 The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Example 1

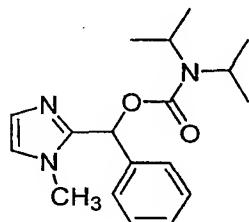


15 To a suspension of 1-benzylimidazole (315 mg, 2.0 mmol) in acetonitrile (3 mL) at 0°C and under nitrogen was added rapidly dropwise a solution of diisopropylcarbamyl chloride (396 mg, 2.4 mmol) in acetonitrile (5 mL). To the slightly cloudy solution was added benzaldehyde (0.31 mL, 3.0 mmol), followed by *N,N*-diisopropylethylamine (1.1 mL, 6.3 mmol). The ice bath was removed

and after stirring for 10 min, the cloudy yellow solution was refluxed for 24h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, 5 and concentrated to yield a pale yellow oil (1.01 g). Flash chromatography on silica (50 mm X 7 in) eluted with ethyl acetate-hexanes (1:1) yielded the product as white crystals.

Yield: 611 mg, 78%
mp 106-109°C;
10 MS (ESP) m/z 392 (MH⁺)

Example 2



15 To a solution of 1-methylimidazole (1.64 g, 20 mmol) and diisopropylcarbamyl chloride (3.6 g, 22 mmol) in acetonitrile (30 mL) at room temperature and under nitrogen was added dropwise benzaldehyde (3.1 mL, 30 mmol), followed by *N,N*-diisopropylethylamine (10 mL, 60 mmol). The resulting mixture was stirred at room temperature for 24, and then 20 concentrated in vacuo. The residue was purified by flash chromatography on silica (BIOTAGE, FLASH 40i, Charlottesville, VA, USA) eluted with ethyl acetate-hexanes (1:1) to yield the title product as white crystals.

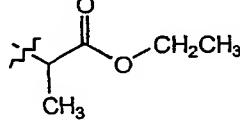
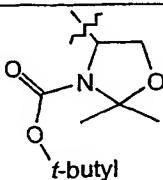
Yield: 6 g, 95%
mp 67-68 °C;
25 MS (ESP) m/z 317 (MH⁺)

Examples 3-29

Selected compounds listed in Table 1 were similarly prepared following the procedure outlined in Example 1 and Example 2, with appropriate selection and substitution of reagents, as listed in Table 2.

5

TABLE 1

Ex #	R ¹⁰	R ¹¹	R ¹²	Z	R ³	R ⁴
3	H	H	benzyl	OC(O)N(i-propyl) ₂	H	t-butyl
4	H	H	benzyl	OC(O)N(i-propyl) ₂	H	i-propyl
5	H	H	benzyl	OC(O)N(i-propyl) ₂	H	cyclohexyl
6	H	H	benzyl	OC(O)N(i-propyl) ₂	H	phenylethyl
7	H	H	benzyl	OC(O)N(i-propyl) ₂	H	benzyl
8	H	H	benzyl	OC(O)N(i-propyl) ₂	H	4-methoxyphenyl
9	H	H	benzyl	OC(O)N(i-propyl) ₂	H	4-methoxyphenyl
10	H	H	benzyl	OC(O)N(i-propyl) ₂	H	4-chlorophenyl
11	H	H	benzyl	OC(O)N(i-propyl) ₂	CF ₃	phenyl
12	H	H	benzyl	OC(O)N(i-propyl) ₂	-C(O)O-CH ₂ CH ₃	
13	H	H	benzyl	OC(O)N(i-propyl) ₂	H	-CH=CH ₂
14	H	H	benzyl	OC(O)N(i-propyl) ₂	H	

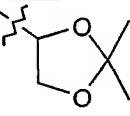
15	H	H	benzyl	OC(O)N(<i>i</i> -propyl) ₂	H	
16	H	H	benzyl	N(phenyl)-C(O)-N(<i>i</i> -propyl) ₂	H	phenyl
17	H	H	benzyl	N(SO ₂ phenyl)-C(O)-N(<i>i</i> -propyl) ₂	H	phenyl
18	H	H	methyl	-OC(O)N(<i>i</i> -propyl) ₂	H	phenyl
19	H	Cl	methyl	-OC(O)N(<i>i</i> -propyl) ₂	H	phenyl
20	H	H	Phenyl	-OC(O)N(<i>i</i> -propyl) ₂	H	phenyl
21	Cl	Cl	methyl	-OC(O)N(<i>i</i> -propyl) ₂	H	phenyl
22	H	H	methyl	-OC(O)N(ethyl) ₂	H	phenyl
23	H	H	methyl	-OC(O)N(methyl) ₂	H	phenyl
24	H	H	methyl	-OC(O)N(<i>i</i> -propyl) ₂	H	ethyl
25	H	H	methyl	-OC(O)N(<i>i</i> -propyl) ₂	H	-CH=CHCH ₃
26	H	H	methyl	-OC(O)N(methyl) ₂	H	2-pyridinyl
27	H	H	methyl	-OC(O)N(methyl) ₂	H	-C(O)-phenyl
28	H	H	methyl	-OC(O)N(methyl) ₂	-C(O)O-CH ₂ CH ₃	phenylethyl
29	H	C(O)OC H ₃	methyl	-OC(O)N(methyl) ₂	H	phenyl

TABLE 2-Preparation Conditions

Ex #	Reaction Temp (°C)	Reflux Time (h)	Yield (%)	mp (°C)	mass spec (MH ⁺)
3	reflux	24	66	48-52	372
4	room temp	66	85	oil	358
5	room temp	24	56	oil	398
6	room temp	29	75	73-78	420
7	reflux	20	32	oil	406
8	reflux	21	30	oil	277 M ⁺ w/loss of OC(O)(<i>i</i> -propyl) ₂

9	room temp	67	73	oil	277 M ⁺ w/loss of OC(O)(i-propyl) ₂
10	room temp	30	77	113-115	426
11	room temp	72	89	124-126	460
12	room temp	68	73	oil	488
13	room temp	68	67	oil	342
14	room temp	72	76	oil	515
15	room temp	144	79	oil	416
16	reflux	21	12	oil	467
17	room temp	72	88	132-139	531
18	room temp	24	90	67-68	316
19	50	24	66	oil	350
20	room temp	24	86	104-105	378
21	reflux	20	42	118-118.5	384
22	60	20	91	oil	288
23	60	20	93	102-102	260
24	room temp	48	96	oil	268
25	room temp	48	65	oil	280
26	room temp	20	78	oil	261
27	room temp	20	70	92-93	288
28	room temp	20	60	112-113	360
29	room temp	48	80	134-135	318

Examples 30-32

- Selected compounds listed in Table 3 were similarly prepared following
 5 the procedure outlined in Example 1, with appropriate selection and substitution of reagents, as listed in Table 4. Note that the conditions as disclosed in Example 31 yielded a mixture of compounds are defined below.

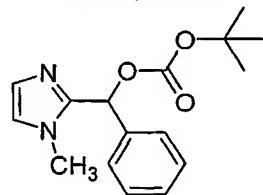
TABLE 3

Ex #	Z	R ³	R ⁴
30	-OC(O)O(<i>t</i> -butyl)	H	phenyl
31	-OC(O)O(<i>t</i> -butyl)	H	phenyl
	-OC(O)(phenyl)	H	phenyl
32	-OC(O)(<i>t</i> -butyl)	H	phenyl

TABLE 4-Preparation Conditions

Ex #	Reaction T (°C)	Reflux Time (h)	Yield (%)	mp (°C)	mass spec (MH ⁺)
30	room temp	23	44	77-79	365
31	reflux	21	52	75-79	365
			11	oil	369
32	reflux	21	32	oil	349

5

Example 33

- To a solution of 1-methylimidazole (164 mg, 2.0 mmol) in anhydrous acetonitrile (5 mL) at room temperature and under nitrogen was added 10 dropwise benzaldehyde (0.31 mL, 3.0 mmol) and a solution of di-*tert*-butyl dicarbonate (480 mg, 2.2 mmol) in anhydrous acetonitrile (1 mL). The mixture was stirred at room temperature for 3 hours, then concentrated in vacuo. The

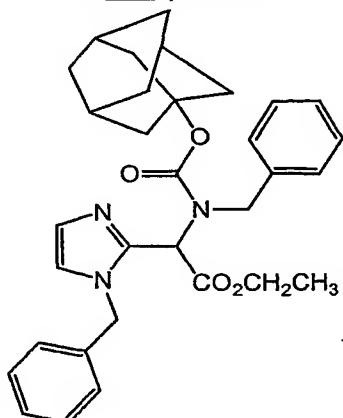
residue was purified by flash chromatography on silica eluted with ethyl acetate-hexanes (2:3) to yield the title product as white crystals.

Yield: 421 mg, 77%

mp 95-96 °C;

5 MS (ESP) m/z 289 (MH⁺)

Example 34



10 To a solution of 1-benzylimidazole (313 mg, 2.0 mmol) in anhydrous acetonitrile (2 mL) at room temperature and under nitrogen was added dropwise a solution of adamantylfluoroformate (498 mg, 2.5 mmol) in anhydrous acetonitrile (2 mL), a solution of benzyliminoacetic acid ethyl ester (573 mg, 3.0 mmol) in anhydrous acetonitrile (2 mL), and diisopropylethyl
15 amine (1.1. mL, 6.3 mmol). The mixture was stirred at room temperature for 16 hours, then concentrated in vacuo. The residue was purified by flash chromatography on silica eluted with ethyl acetate-hexanes (1:3) to yield the title product as white crystals.

Yield: 441 mg, 42%

20 mp 83-85 °C;

MS (ESP) m/z 538 (MH⁺)

Examples 35-40

Selected compounds listed in Table 5 were similarly prepared following the procedure outlined in Example 1, Example 2 and Example 33 with appropriate selection and substitution of reagents, as listed in Table 6.

5

Table 5

Ex #	Z	R ³	R ⁴
35	-N(C(O)N(i-propyl) ₂)OC(O)CH ₃	H	phenyl
36	-N(benzyl)C(O)N(i-propyl) ₂	H	phenyl
37	-N(benzyl)C(O)N(i-propyl) ₂	H	phenyl
38	-N(SO ₂ phenyl)C(O)O-t-butyl	H	phenyl
39	-N(SO ₂ -p-toluenyl)C(O)O-t-butyl	methyl	phenyl
40	-N(benzyl)C(O)O-t-butyl	H	-C(O)O-ethyl

TABLE 6

Ex #	Reaction T (°C)	Reaction Time (h)	Yield (%)	mp (°C)	mass spec (MH ⁺)
35	room temp	16	60	oil	248 M ⁺ w/loss of C(O)N(i-propyl) ₂
36	room temp	15	65	oil	248 M ⁺ w/loss of C(O)N(i-propyl) ₂
37	room temp	15	45	oil	248 M ⁺ w/loss of C(O)N(i-propyl) ₂
38	room temp	3	60	51-52	503
39	room temp	3	35	56-57	531
40	room temp	3	55	oil	449

Examples 41-50

Selected compounds listed in Table 7 and Table 8 were similarly prepared following the procedure outlined in Example 1, Example 2 and Example 33, with appropriate selection and substitution of reagents, as listed in Table 9

TABLE 7

Ex #	Z	R ³	R ⁴		
41	OC(O)N(<i>i</i> -propyl) ₂	H	phenyl		
Ex #	Z	R ¹⁰	R ¹¹	R ³	R ⁴
42	OC(O)N(<i>i</i> -propyl) ₂	H	H	H	phenyl
43	-OC(O)N(<i>i</i> -propyl) ₂	H	H	H	phenyl
44	-OC(O)N(<i>i</i> -propyl) ₂	H	H	H	<i>p</i> -nitrophenyl
45	-OC(O)N(<i>i</i> -propyl) ₂	H	H	CF ₃	phenyl
46	-OC(O)N(<i>i</i> -propyl) ₂	CH ₃	CH=CH ₂	H	phenyl
47	-OC(O)N(<i>i</i> -propyl) ₂	CH ₃	CH ₃	H	phenyl
48	-OC(O)O-t-butyl	H	H	H	phenyl
49	-OC(O)NMe ₂	H	H	H	phenyl

10

TABLE 8

--

Ex #	Z	R ³	R ⁴
50	-OC(O)N(methyl) ₂	H	phenyl

TABLE 9 – Preparation Conditions

Ex #	Reaction T (°C)	Reflux Time (h)	Yield (%)	mp (°C)	mass spec (MH ⁺)
41	reflux	23	88	126-128	366
42	reflux	22	39	70-71	319
43	reflux	52	17	65-68	319
44	room temp	48	42	oil	364
45	room temp	48	55	82-82	387
46	reflux	24	42	oil	359
47	reflux	24	46	98-99	347
48	60	20	65	oil	292
49	60	20	61	45-47	263
50	60	20	41	oil	313

5

Examples 51-52

Selected compounds listed in Table 10 were similarly prepared following the procedure outlined in Example 2, with appropriate selection and substitution of reagents, as listed in Table 11.

10

TABLE 10

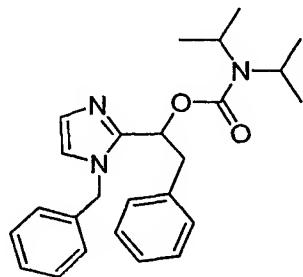
Ex #	Z	R ³	R ⁴
51	-OC(O)N(<i>i</i> -propyl) ₂	H	phenyl

Ex #	Z	R ³	R ⁴
52	-OC(O)N(<i>i</i> -propyl) ₂	H	phenyl

TABLE 11– Preparation Conditions

Ex #	Reaction T (°C)	Time (h)	Yield (%)	mp (°C)	mass spec (MH ⁺)
51	room temp	23	68	115-116	393
52	room temp	22	66	93-94	393

5

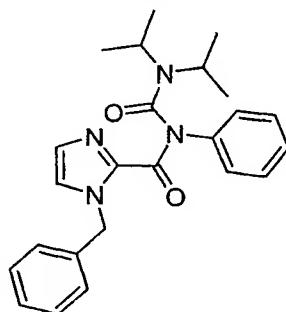
Example 53

To a suspension of 1-benzylimidazole (317 mg, 2.0 mmol) in acetonitrile (3 mL) at room temperature was added rapidly dropwise a solution of 10 diisopropylcarbamyl chloride (396 mg, 2.4 mmol) in acetonitrile (5 mL). To the slightly cloudy solution was added phenylacetaldehyde (0.35 mL, 3.0 mmol), followed by *N,N*-diisopropylethylamine (1.1 mL, 6.3 mmol). The mixture was refluxed for 5.5h and cooled to room temperature. To the resulting mixture was then added a solution of diisopropylcarbamyl chloride (396 mg, 2.4 mmol) in 15 acetonitrile (5 mL), followed by phenylacetaldehyde (0.35 mL, 3.0 mmol) and *N,N*-diisopropylethylamine (1.1 mL, 6.3 mmol). The reaction mixture was refluxed for 24h, cooled to room temperature, and then charged again with a

solution of diisopropylcarbamyl chloride (396 mg, 2.4 mmol) in acetonitrile (5 mL), followed by phenylacetaldehyde (0.35 mL, 3.0 mmol) and *N,N*-diisopropylethylamine (1.1 mL, 6.3 mmol). The mixture was refluxed for an additional 21h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to a yellow oil (2.70 g). Flash chromatography on silica (50 mm X 8 in) eluted with 40% ethyl acetate in hexanes yielded the product as pale yellow crystals.

10 Yield: 632 mg, 78%
mp 75-79 °C;
MS (ESP) m/z 406 (MH⁺)

15

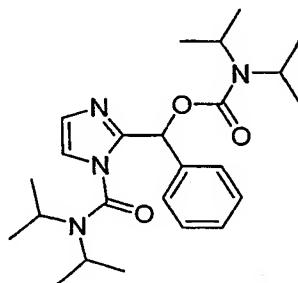
Example 54

To a suspension of 1-benzylimidazole (317 mg, 2.0 mmol) in acetonitrile (3 mL) at room temperature and under nitrogen was added rapidly dropwise a solution of diisopropylcarbamyl chloride (391 mg, 2.4 mmol) in acetonitrile (5 mL). To the slightly cloudy solution was added phenylisocyanate (0.33 mL, 3.0 mmol), followed by *N,N*-diisopropylethylamine (1.1 mL, 6.3 mmol). The mixture was refluxed for 21h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a yellow oil (1.22 g). Flash chromatography on silica (50 mm X 6 in) eluted with 25% ethyl acetate in hexanes yielded a crystalline solid product (1.0 g) containing an impurity. Flash

chromatography of this material on silica (50 mm X 6 in) eluted with 20% acetone in hexanes yielded a pale yellow foam (825 mg). The foam was recrystallized from ethyl acetate/hexanes to yield the title product as white crystals.

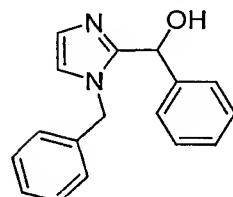
- 5 Yield: 577 mg, 71%
mp 125.5-127°C;
MS (ESP) m/z 405 (MH⁺)

10

Example 55

To a suspension of imidazole (140 mg, 2.0 mmol) in acetonitrile (3 mL) at room temperature and under nitrogen was added rapidly dropwise a solution of diisopropylcarbamyl chloride (786 mg, 4.8 mmol) in acetonitrile (5 mL). To
15 the mixture was added benzaldehyde (0.31 mL, (3.0 mmol), followed by *N,N*-diisopropylethylamine (1.5 mL, 8.6 mmol). The reaction mixture was refluxed for 22h, cooled to room temperature, and concentrated in vacuo. The residue was dissolved in ethyl acetate and washed successively with dilute brine (2X) and saturated brine. The organic layer was dried over magnesium sulfate,
20 filtered, and concentrated to a yellow solid (1.19 g). Flash chromatography on silica (50 mm X 6 in) eluted with 45% ethyl acetate in hexanes yielded the product as white crystals.

- Yield: 536 mg, 61%
mp 173-175 °C;
25 MS (ESP) m/z 429 (MH⁺)

Example 56

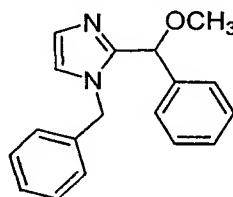
A solution of the product prepared in Example 1 (392 mg 1.0 mmol) in tetrahydrofuran (5 mL), water (1 mL), and trifluoroacetic acid (0.5 mL) was
 5 refluxed for 11h. After cooling, the reaction mixture was diluted with 1:1 ethyl acetate/ethyl ether and washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a white solid. Flash chromatography on silica (25 mm X 7 in) eluted with 5% methanol in methylene chloride yielded the product
 10 as white crystals.

Yield: 222 mg, 84%

mp 111-114 °C;

MS (ESP) m/z 265 (MH⁺)

15

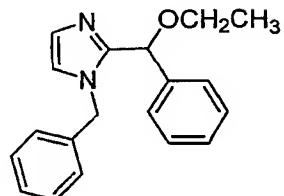
Example 57

A solution of the product prepared in Example 1 (391 mg, 1.0 mmol) in anhydrous methanol (5 mL) and trifluoroacetic acid (0.5 mL) under a nitrogen atmosphere was refluxed for 28h. After cooling, trifluoroacetic acid (0.5 mL)
 20 was added and the refluxing continued for 24h. After cooling, the reaction mixture was diluted with 1:1 ethyl acetate/ethyl ether and washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a white film. Flash chromatography on silica (25 mm X 7 in) eluted with 80% ethyl acetate in
 25 hexanes yielded the product as pale yellow crystals.

Yield: 167 mg, 60%
mp 68-71.5 °C;
MS (ESP) m/z 279 (MH⁺)

5

Example 58

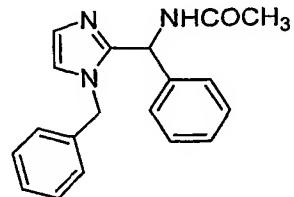


A solution of the product prepared in Example 1 (781 mg, 2.0 mmol) in anhydrous ethanol (10 mL) and trifluoroacetic acid (0.5 mL) under a nitrogen atmosphere was refluxed for 8h. After cooling, the reaction mixture was concentrated, diluted with ethyl acetate and then washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a yellow oil (0.77 g). Flash chromatography on silica (50 mm X 6 in) eluted with 60% ethyl acetate in hexanes yielded the product as a colorless oil.

Yield: 492 mg, 84%
MS (ESP) m/z 293 (MH⁺)

20

Example 59



A solution of the product prepared in Example 1 (787 mg, 2.0 mmol) and acetamide (1.18 g, 20 mmol) in tetrahydrofuran (10 mL) and trifluoroacetic acid (0.5 mL) under a nitrogen atmosphere was refluxed for 18h. After cooling, the reaction mixture was diluted with 1:1 ethyl acetate/ethyl ether and washed successively with 2N NaOH, water, and saturated brine. The organic layer was

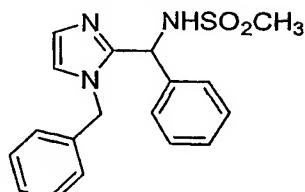
dried over magnesium sulfate, filtered, and concentrated to yield a white solid (555 mg). The solid was recrystallized from ethyl acetate/hexanes to yield the title product as white crystals.

Yield: 385 mg, 63%

5 mp 171-176 °C;

MS (ESP) m/z 306 (MH⁺)

Example 60



10

A solution of the product prepared in Example 1 (784 mg, 2.0 mmol) and methanesulfonamide (1.90 g, 20 mmol) in tetrahydrofuran (10 mL) and trifluoroacetic acid (0.5 mL) under a nitrogen atmosphere was refluxed for 24h. After cooling, the reaction mixture was concentrated, diluted with 1:1 ethyl acetate/ethyl ether and then washed successively with 1N sodium carbonate, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a white film (0.75 g). Flash chromatography on silica (50 mm X 6 in) eluted with 4% methanol in methylene chloride yielded the product as white crystals.

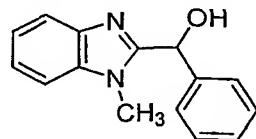
15 Yield: 514 mg, 75%

mp 162-163 °C;

MS (ESP) m/z 342 (MH⁺)

25

Example 61

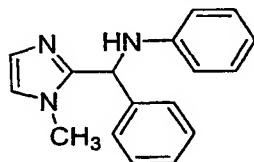


A solution of the product prepared in Example 40 (364 mg, 1.0 mmol) in tetrahydrofuran (5 mL), water (1 mL) and trifluoroacetic acid (0.5 mL) was refluxed for 18h. After cooling, the reaction mixture was diluted with ethyl acetate and washed successively with 1N sodium carbonate, water, and 5 saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield white crystals. Flash chromatography on silica (25 mm X 8 in) eluted with 3% methanol in methylene chloride yielded the product as white crystals.

Yield: 148 mg, 62%

10 mp 160.5-162 °C;
MS (ESP) m/z 239 (MH⁺)

Example 62



15

To a solution of the product prepared in Example 2 (158 mg, 0.5 mmol) in anhydrous THF (5 mL) and trifluoroacetic acid (0.22 mL, 3 mmol) under a nitrogen atmosphere was added aniline (0.47 mL, 5 mmol). The resulting mixture was refluxed for 4 h. After cooling, the reaction mixture was diluted 20 with dichloromethane and washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a yellow oil. Flash chromatography on silica (20 mm X 6 in) eluted with 50% ethyl acetate in hexanes yielded the product as light yellow crystals.

25 Yield: 102 mg, 81%
mp 110-112°C;
MS (ESP) m/z 264 (MH⁺)

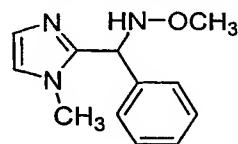
Example 63

- To a solution of the product prepared in Example 2 (158 mg, 0.5 mmol) in anhydrous THF (5 mL) and trifluoroacetic acid (0.33 mL, 4.5 mmol) under a nitrogen atmosphere was added piperidine (0.5 mL, 5 mmol) and $\text{BF}_3\bullet\text{Et}_2\text{O}$ (0.1 mL, 0.75 mmol) successively. The resulting mixture was refluxed for 4. After cooling, the reaction mixture was diluted with dichloromethane and washed successively with 2N NaOH, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a yellow oil.
- Flash chromatography on silica (20 mm X 6 in) eluted with 5% methanol in ethyl acetate yielded the product as a light yellow oil.

Yield: 109 mg, 85%

MS (ESP) m/z 256 (MH^+)

15

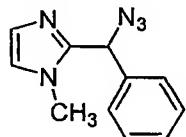
Example 64

- To a suspension of the product prepared in Example 2 (158 mg, 0.5 mmol) and $\text{H}_2\text{NOMe}\bullet\text{HCl}$ (555 mg, 5 mmol) in anhydrous THP (5 mL) under a nitrogen atmosphere was added $\text{BF}_3\bullet\text{Et}_2\text{O}$ (0.2 mL, 1.5 mmol). The resulting mixture was refluxed for 4. After cooling, the reaction mixture was filtered. The filtrate was dissolved in 10% methanol in dichloromethane, and washed successively with saturated NaHCO_3 , water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a yellow oil. Flash chromatography on silica (20 mm X 6 in) eluted with 10% methanol in dichloromethane yielded the product as white crystals.

Yield: 80 mg, 73%

mp 119-122 °C;
MS (ESP) m/z 218 (MH⁺)

5

Example 65

To a solution of the product prepared in Example 2 (158 mg, 0.5 mmol) in anhydrous DMF (5 mL) under a nitrogen atmosphere was added NaN₃ (98 mg, 1.5 mmol) and pyridinium p-toluenesulfonate (catalytic amount). The 10 resulting mixture was stirred at 70 °C overnight. After cooling, the reaction mixture was diluted with dichloromethane and washed successively with saturated NaHCO₃, water, and saturated brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a yellow oil. Flash chromatography on silica (20 mm X 6 in) eluted with 2% methanol in ethyl acetate yielded the product as a oil.

Yield: 85 mg, 80%
MS (ESP) m/z 214 (MH⁺)

20

Examples 66-79

Selected compounds listed in Table 12 were similarly prepared following the procedure outlined in Example 62 to 65, with appropriate selection and substitution of reagents, as listed in Table 13.

25

TABLE 12

Ex #	Z	R ¹²	R ³	R ⁴

66	morpholin-1-yl	CH ₃	H	phenyl
67	-S-phenyl	CH ₃	H	phenyl
68	-NH-pyridin-2-yl	CH ₃	H	phenyl
69	-NH(CH ₂ CH ₂ OH)	CH ₃	H	phenyl
70	-S-CH ₂ CH ₂ NH ₂	CH ₃	H	phenyl
71	-NH-benzyl	CH ₃	H	phenyl
72	4-methyl piperazin-1-yl	CH ₃	H	phenyl
73	imidazol-1-yl	CH ₃	H	phenyl
74	-NH-phenyl	CH ₃	H	ethyl
75	-NH-phenyl	CH ₃	H	-CH=CH ₂ CH ₃
76	piperidin-1-yl	CH ₃	H	-CH=CH ₂ CH ₃
77	morpholin-1-yl	CH ₃	H	-CH=CH ₂ CH ₃
78	morpholin-1-yl	CH ₃	H	ethyl
Ex #	Z	R ³	R ⁴	
79	piperidin-1-yl	H	phenyl	

TABLE 10 – PREPARATION CONDITIONS

Ex #	reaction T (°C)	reflux time (h)	yield (%)	mp (°C)	mass spec (MH ⁺)
66	reflux	15	82	oil	258
67	reflux	6	86	oil	281
68	reflux	3	85	oil	265
69	reflux	20	65	oil	232
70	reflux	20	70	oil	249
71	reflux	24	76	oil	278
72	reflux	20	81	oil	271
73	reflux	20	75	oil	234
74	reflux	72	74	oil	216
75	reflux	4	88	122-123	228

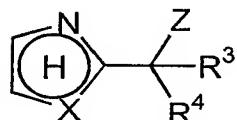
76	reflux	4	60	oil	220
77	reflux	4	68	oil	222
78	reflux	72	40	oil	210
79	reflux	20	50	oil	259

While some the previous examples describe the purification of reaction products by flash chromatography, these reaction products can also be purified in 5 a high-throughput mode using high-throughput reverse-phase or high-throughput normal phase HPLC instruments, thereby, increasing the efficiency of compounds library syntheses.

While the foregoing specification teaches the principles of the present 10 invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

We Claim:

1. A method of synthesizing highly substituted azole compounds having the general formula (Ia):

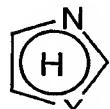


5

(Ia)

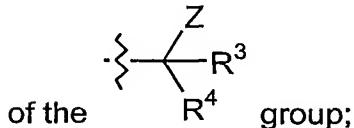
wherein

X is selected from the group consisting of NH, NR^A and S;



represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group consisting of N, O and S;

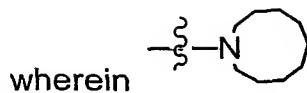
provided that the additional heteroatoms are not at the attachment point



of the group;
provided that the 5 membered ring remains aromatic in nature;
wherein the 5 membered ring is optionally substituted with one to three
15 substituents independently selected from the group consisting of halogen,
hydroxy, alkyl, halogenated alkyl, alkenyl, cycloalkyl, alkoxy, aryl, aralkyl,
heterocyclyl, amino, mono-or di-substituted amino, cyano nitro, -COOR, -COR,
-SO₂R and -CONR^BR^C; wherein the amine substituents are independently
selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or
20 heterocyclyl may be further optionally substituted with one or more substituent
is independently selected from halogen, hydroxy, alkyl, halogenated alkyl,
alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

Z is selected from the group consisting of -OR^A, -NR^AR^B, -N(R^A)OR^B, -





wherein represents a three to eight membered heterocyclyl

group bound at the N atom, wherein the heterocyclyl group is saturated, partially unsaturated or aromatic; when the heterocyclyl group is a saturated six to eight membered heterocyclyl, the heterocyclyl group may optionally contain

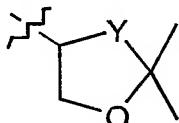
- 5 a group selected from O, CHR, NR, S, SO, or SO₂, provided that that the group is separated from the N atom by at least two carbon atoms; and wherein the heterocyclyl group is optionally substituted with one or more substituents independently selected from R;

R³ is selected from the group consisting of hydrogen, alkyl, aralkyl,

- 10 cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aralkyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

R⁴ is selected from the group consisting of, alkyl, aryl, aralkyl, cycloalkyl,

- 15 fluorinated alkyl, alkenyl, alkynyl, -COOR, -COR, -CONR^CR^D, -alkyl-COOR,



heterocyclyl and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono-or di-substituted amino, cyano or nitro; and where Y is

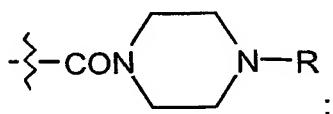
- 20 selected from the group consisting of O, S and NR^A;

where R is selected from the group consisting of alkyl, aryl, aralkyl,

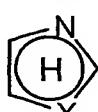
cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated

- 25 alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and

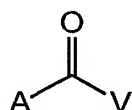


- where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocycl ring structure;
- 5 which method comprises reacting a compound of formula (III)



(III)

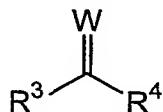
- 10 with a compound of formula (IV)



(IV)

wherein A is selected from F, Cl, Br or $-OC(O)-t\text{-butyl}$, and wherein V is a sterically hindered group, in a non-protic solvent;

and then reacting with a compound of formula (V)

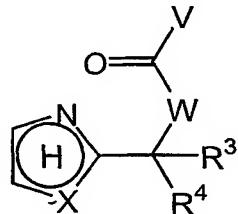


(V)

15

wherein W is selected from the group consisting of $-O-$, $-NSO_2R$, $-NSOR$, $-NCOR$, $-NCOOR$, $-NCOR^CR^D$ and $-NR$

to form the corresponding compound of formula (Ic)



(Ic)

and optionally reacting the compound of formula (Ic) with a compound of formula (VI)

Z-H

(VI)

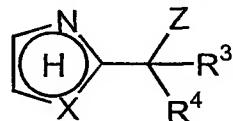
wherein Z is as previously defined, to yield the corresponding compound
5 of formula (Ia).

2. The process of Claim 1 wherein V is selected from the group consisting of t-butyl, O-t-butyl, O-isopropyl, O-adamantyl, adamantyl, N(alkyl)₂, N(aryl)₂, 2,6-dimethylphenyl, 2,6-disubstituted phenyl.

10

3. The process of Claim 1 wherein the non-protic solvent is selected from the group consisting of acetonitrile, dioxane and THF.

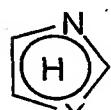
4. A process for preparing a compound of general formula (Ia):



15 (Ia)

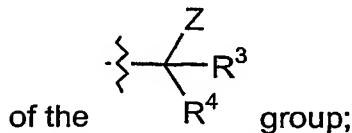
wherein

X is selected from the group consisting of NH, NR^A and S;



represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group
20 consisting of N, O and S;

provided that the additional heteroatoms are not at the attachment point



of the group;

provided that the 5 membered ring remains aromatic in nature;

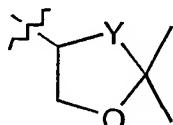
wherein the 5 membered ring is optionally substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, alkenyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -

- 5 COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

10 Z is hydrogen;

R³ is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aralkyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

15 R⁴ is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, -COOR, -COR, -CONR^CR^D, -alkyl-COOR,

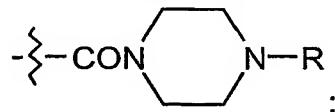


heterocyclyl and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents

- 20 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono-or di-substituted amino, cyano or nitro; and where Y is selected from the group consisting of O, S and NR^A;

where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the 25 aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

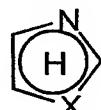
where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



- 5 where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocyclil ring structure;

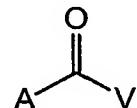
10

which method comprises reacting a compound of formula (III)



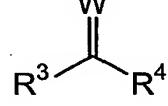
(III)

with a compound of formula (IV)



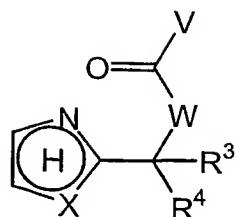
(IV)

- 15 wherein A is selected from F, Cl, Br or -OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent; and then reacting with a compound of formula (V)



(V)

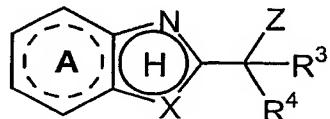
- wherein W is selected from the group consisting of O, NSO₂R, -NSOR, -NCOR, -NCOOR, -NCOR^CR^D, -NOCOR and NR to form the corresponding compound of formula (Ic)



and reacting the compound of formula (Ic) with hydrogen gas, in the presence of a metal catalyst, to yield the corresponding compound of formula (Ia).

5

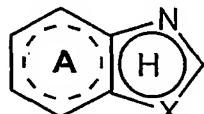
5. A method of synthesizing highly substituted azole compounds having the general formula (IIa):



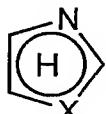
(IIa)

wherein

10 X is selected from the group consisting of NH, NR^A and S;



represents a 9 membered ring structure, wherein the five



membered portion of the ring structure - - is aromatic and the six



membered portion of the ring structure - - is saturated, partially unsaturated, or aromatic;

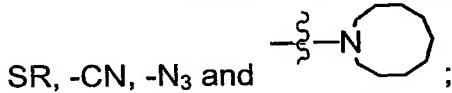
15 wherein the 5 membered portion of the ring structure is optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents

are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

- 5 wherein the 6-membered portion of the ring structure may further
optionally containing one to four additional heteroatoms selected from the
group consisting of N, O and S;

wherein the 6-membered portion of the ring structure may further be
optionally substituted with one to four substituents independently selected from
10 the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl,
alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano,
nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents
are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the
cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or
15 more substituent independently selected from halogen, hydroxy, alkyl,
halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

Z is selected from the group consisting of -OR^A, -NR^AR^B, -N(R^A)OR^B, -

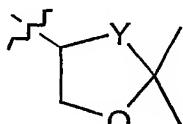


wherein  represents a three to eight membered heterocyclic

- 20 group bound at the N atom, wherein the heterocyclyl group is saturated, partially unsaturated or aromatic; when the heterocyclyl group is a saturated six to eight membered heterocyclyl, the heterocyclyl group may optionally contains a group selected from O, CHR, NR, S, SO, or SO₂, provided that that the group is separated from the N atom by at least two carbon atoms; and wherein the
25 heterocyclyl group is optionally substituted with one or more substituents independently selected from R;

R^3 is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aralkyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;

R^4 is selected from the group consisting of, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, -COOR, -COR, -CONR^CR^D, -alkyl-COOR,



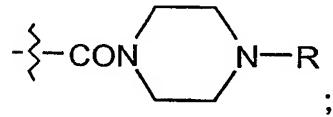
heterocyclyl and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents

- 5 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono-or di-substituted amino, cyano or nitro; and where Y is selected from the group consisting of O, S and NR^A;

where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the

- 10 aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and

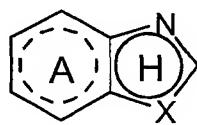


15

where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl,

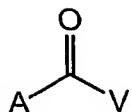
- 20 halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocyclyl ring structure;

which method comprises reacting a compound of formula (VII)



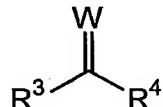
(VII)

- 25 with a compound of formula (IV)



(IV)

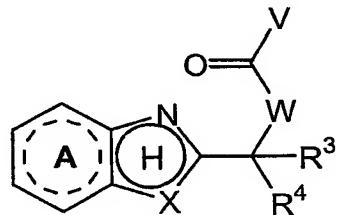
wherein A is selected from F, Cl, Br or OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent;
and then reacting with a compound of formula (V)



(V)

5

wherein W is selected from the group consisting of O, NSO_2R , - NSOR , - NCOR , - NCOOR , - NCOR^CR^D , - NOCOR and NR
 to form the corresponding compound of formula (IIc)



(IIc)

10 and optionally reacting the compound of formula (IIc) with a compound
of formula (VI)

Z-H

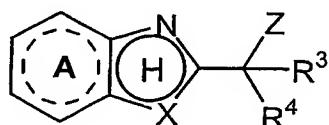
(VI)

wherein Z is as previously defined, to yield the corresponding compound of formula (IIa).

15

6. The process of Claim 5 wherein V is selected from the group consisting of t-butyl, O-t-butyl, O-isopropyl and O-adamantyl, adamantyl, N(alkyl)₂, N(aryl)₂, 2,6-dimethylphenyl, 2,6-disubstituted phenyl.

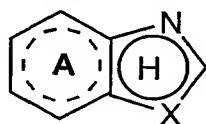
7. The process of Claim 5 wherein the non-protic solvent is selected from the group consisting of acetonitrile, dioxane and THF.
- 5 8. A method of synthesizing highly substituted azole compounds having the general formula (IIa):



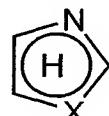
(IIa)

wherein

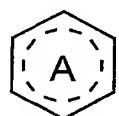
X is selected from the group consisting of NH, NR^A and S;



represents a 9 membered ring structure, wherein the five



10 membered portion of the ring structure - - is aromatic and the six

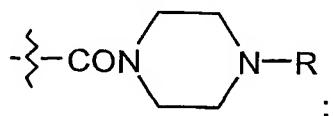


membered portion of the ring structure - - is saturated, partially unsaturated, or aromatic;

wherein the 5 membered portion of the ring structure is optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; wherein the 6-membered portion of the ring structure may further optionally containing one to four additional heteroatoms selected from the group consisting of N, O and S;

- wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano, 5 nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- 10 Z is hydrogen;
- R³ is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated 15 alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- R⁴ is selected from the group consisting of, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, -COR, -COOR, -CONR^CR^D, -alkyl-COOR,
-
- heterocyclyl and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents 20 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono-or di-substituted amino, cyano or nitro; and where Y is selected from the group consisting of O, S and NR^A;
- where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the 25 aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



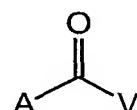
- where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocycl ring structure;
- 10

which method comprises reacting a compound of formula (VII)



(VII)

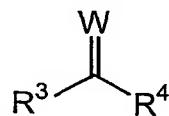
with a compound of formula (IV)



(IV)

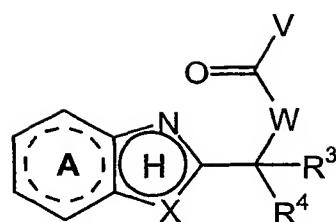
- 15 wherein A is selected from F, Cl, Br or OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent;

and then reacting with a compound of formula (V)



(V)

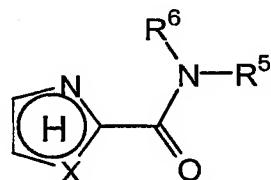
- wherein W is selected from the group consisting of O, NSO₂R, -NSOR, -NCOR, -NCOOR, -NCOR^CR^D, -NOCOR and NR, to form the corresponding compound of formula (IIc)



and optionally reacting the compound of formula (IIc) with hydrogen gas, in the presence of a metal catalyst, to yield the corresponding compound of formula (IIa).

5

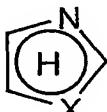
9. A method for preparing compounds of the formula (Ib)



(Ib)

wherein

X is selected from the group consisting of NH, NR^A and S;



10 represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group consisting of N, O and S;

provided that the additional heteroatoms are not at the attachment point of the -C(O)NR⁵R⁶ group;

- 15 provided that the 5 membered ring remains aromatic in nature; wherein the 5 membered ring is optionally substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, alkenyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclil, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the

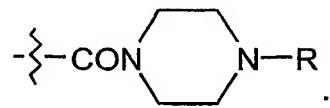
cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

R^5 is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl,

- 5 cycloalkyl, fluorinated alkyl and heterocyclyl; wherein the aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

R^6 is selected from the group consisting of hydrogen, alkyl, aralkyl,

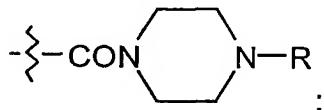
- 10 cycloalkyl, -COOR, -COR, -SO₂R, -CONR^CR^D and



- where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

- 15 alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

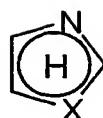
where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



- 20 where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocyclyl ring structure;

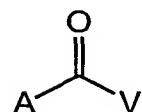
25

which method comprises reacting a compound of formula (III)



(III)

with a compound of formula (IV)



(IV)

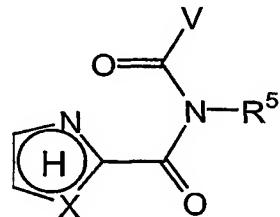
wherein A is selected from F, Cl, Br or OC(O)-t-butyl, and wherein V is a
5 sterically hindered group, in a non-protic solvent;

and then reacting with a compound of formula (VIII)



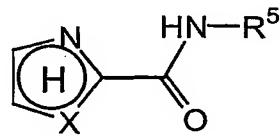
(VIII)

wherein R⁵ is as previously defined, to yield the compound of formula
(Id)



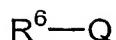
(Id)

10 reacting the compound of formula (I) with an inorganic base to yield the compound of formula (Ie)



(Ie)

optionally reacting the compound of formula (Ie) with a compound of
15 formula (IX)



(IX)

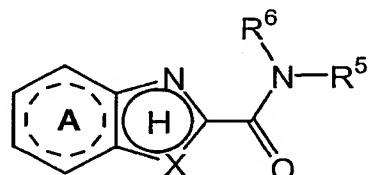
wherein Q is selected from the group consisting of chlorine, bromine and iodine, in the presence of a base, to yield the corresponding compound of formula (Ib).

5

10. The process of Claim 9 wherein V is selected from the group consisting of t-butyl, O-t-butyl, O-isopropyl, O-adamantyl adamantlyl, N(alkyl)₂, N(aryl)₂, 2,6-dimethylphenyl, 2,6-disubstituted phenyl.

10 11. The process of Claim 9 wherein the non-protic solvent is selected from the group consisting of acetonitrile, dioxane and THF.

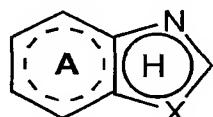
12. A method for preparing compounds of the formula (IIb)



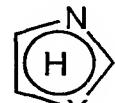
(IIb)

15 wherein

X is selected from the group consisting of NH, NR^A and S;



represents a 9 membered ring structure, wherein the five



membered portion of the ring structure - - is aromatic and the six



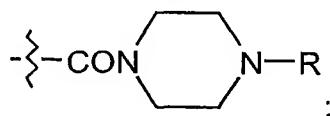
membered portion of the ring structure - - is saturated, partially

20 unsaturated, or aromatic;

- wherein the 5 membered portion of the ring structure is optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano, 5 nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- 10 wherein the 6-membered portion of the ring structure may further optionally containing one to four additional heteroatoms selected from the group consisting of N, O and S;
- wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four substituents independently selected from 15 the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or 20 more substituent independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- R⁵ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocyclyl; wherein the aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents 25 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- R⁶ is selected from the group consisting of hydrogen, alkyl, aralkyl,
- ;
- cycloalkyl, -COOR, -COR, -SO₂R, -CONR^CR^D and
- 30 where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more

substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

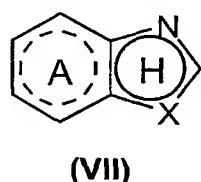
where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



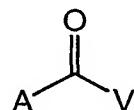
where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl,

- 10
- halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocycl ring structure;

which method comprises reacting a compound of formula (VII)



- 15
- with a compound of formula (IV)



(IV)

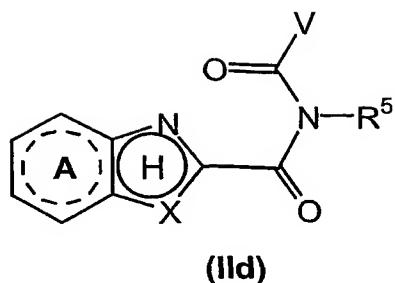
wherein A is selected from F, Cl, Br or OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent;

and then reacting with a compound of formula (VIII)

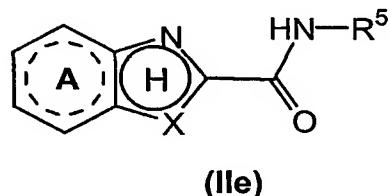


- 20
- (VIII)

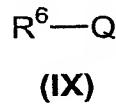
wherein R⁵ is as previously defined, to yield the compound of formula (IId)



reacting the compound of formula (IIId) with an inorganic base to yield the compound of formula (IIe)



- 5 optionally reacting the compound of formula (IIe) with a compound of formula (IX)



- wherein Q is selected from the group consisting of chlorine, bromine and iodine, in the presence of a base, to yield the corresponding compound of
10 formula (IIb).

13. The process of Claim 9 wherein V is selected from the group consisting of t-butyl, O-t-butyl, O-isopropyl, O-adamantyl, adamantyl, N(alkyl)₂, N(aryl)₂, 2,6-dimethylphenyl, 2,6-disubstituted phenyl.

15

14. The process of Claim 9 wherein the non-protic solvent is selected from the group consisting of acetonitrile, dioxane and THF.

15. A chemical library comprising a plurality of substituted azoles
20 compounds prepared by the method of Claim 1.

16. A chemical library comprising a plurality of substituted azoles
compounds prepared by the method of Claim 4.

17. A chemical library comprising a plurality of substituted azoles compounds prepared by the method of Claim 5.

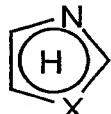
5 18. A chemical library comprising a plurality of substituted azoles compounds prepared by the method of Claim 8.

19. A chemical library comprising a plurality of substituted azoles compounds prepared by the method of Claim 9.

10

20. A chemical library comprising a plurality of substituted azoles compounds prepared by the method of Claim 12.

21. The process of Claim 1 wherein

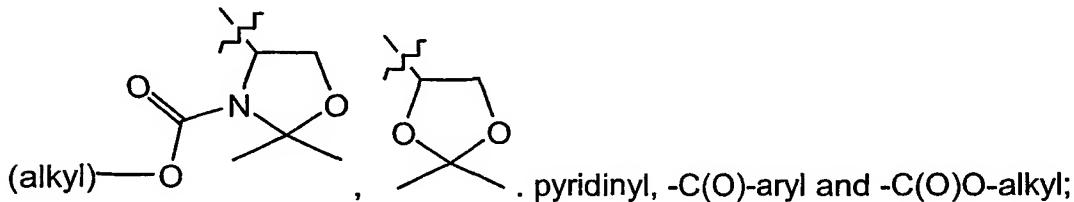


15 is selected from the group consisting of imidazolyl, substituted imidazolyl (wherein the substituents on the imidazolyl group are one or more independently selected from halogen, alkyl, aryl, aralkyl, cycloalkyl, or alkoxy carbonyl, $-C(O)N(alkyl)_2$), thiazolyl, substituted thiazolyl (wherin the substituents on the thiazolyl group are one or more independently selected 20 from alkyl and alkenyl), 2-aralkyl-substituted-4H-1,2,4-triazolyl and 4-aralkyl substituted-4H-1,2,4-triazolyl;

Z is selected from the group consisting of $-OC(O)N(alkyl)_2$, $-N(aryl)C(O)N(alkyl)_2$, $-N(aralkyl)C(O)N(alkyl)_2$, $-N(aralkyl)C(O)O(alkyl)$, $-N(aralkyl)C(O)O$ -adamantyl, $-N(SO_2aryl)C(O)N(alkyl)_2$, $-N(SO_2aryl)C(O)O(alkyl)$, $-N(SO_2alkyl$ substituted aryl $)C(O)O(alkyl)$, $-N(C(O)N(alkyl)_2)OC(O)(alkyl)$, $-OC(O)O(alkyl)$, $-OC(O)(aryl)$, $-OH$, $-alkoxy$, $-N_3$, $-NHC(O)-alkyl$, $-NH(alkyl)$, $-NH(hydroxy substituted alkyl)$, $-NH(alkoxy)$, $-NH(aryl)$, $-NH(aralkyl)$, $-NH-(heterocyclyl)$, $-NHSO_2-alkyl$, $-SH-aryl$, $-SH-alkyl$, $-SH-(amino substituted alkyl)$ and heterocyclyl;

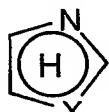
30 R^3 is selected from the group consisting of hydrogen, alkyl, trifluoromethyl and $-C(O)O-alkyl$;

and R⁴ is selected from the group consisting of alkyl, alkenyl, cycloalkyl, aryl, substituted aryl (where the aryl substituent is selected from halogen, alkyl, alkoxy, nitro, amino, alkylamino or dialkylamino), aralkyl, -(alkyl)-C(O)O-(alkyl),



5

22. The process of Claim 21 wherein

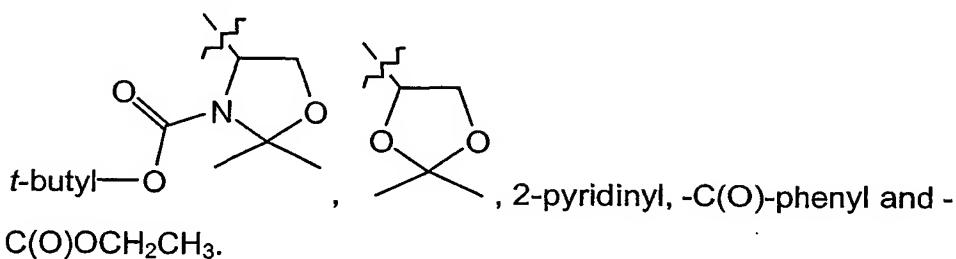
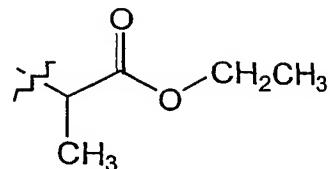


is selected from the group consisting of 1-imidazolyl, 1-methyl-imidazolyl, 1-phenyl-imidazolyl, 1-benzyl-imidazolyl, 1-(di(*i*-propyl)aminocarbonyl)-imidazolyl, 1-methyl-5-chloro-imidazolyl, 1-methyl-4,5-dichloro-imidazolyl, 1-methyl-5-methoxycarbonyl-imidazolyl, thiazolyl, 4,5-dimethyl-thiazolyl, 4-methyl-5-vinyl-thiazolyl, 2-benzyl-4H-1,2,4-triazolyl and 4-benzyl-4H-1,2,4-triazolyl;

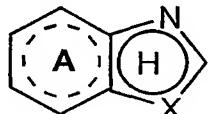
Z is selected from the group consisting of -OC(O)N(methyl)₂, -OC(O)N(ethyl)₂, -OC(O)N(i-propyl)₂, -N(phenyl)C(O)N(i-propyl)₂, -N(benzyl)C(O)O-t-butyl, -N(benzyl)C(O)O-adamantyl, N(benzyl)C(O)N(i-propyl)₂, -N(SO₂-phenyl)C(O)N(i-propyl)₂, -N(SO₂phenyl)C(O)O-t-butyl, -N(SO₂-p-toluenyl)C(O)O-t-butyl, -N(C(O)N(i-propyl)₂)OC(O)methyl, -OC(O)O(t-butyl), -OC(O)(phenyl), -OH, -OCH₃, -OCH₂CH₃, -N₃, -NH-C(O)CH₃, -NH-SO₂CH₃, -NH-OCH₃, -NH-CH₂CH₂OH, -NH-phenyl, -NH-benzyl, -NH-pyridin-2-yl, -S-phenyl, -S-CH₂CH₂NH₂, morpholin-1-yl, piperidin-1-yl, 4-methyl-piperazin-1-yl and imidazol-1-yl;

R³ is selected from the group consisting of hydrogen, methyl, trifluoromethyl and -C(O)OCH₂CH₃;

and R⁴ is selected from the group consisting of methyl, ethyl, t-butyl, i-propyl, cyclohexyl, phenyl, 4-methoxyphenyl, 4-chlorophenyl, 4-nitrophenyl,



5 23. The process of Claim 5 wherein

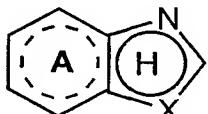


is selected from the group consisting of 1-substituted-benzimidazolyl (where the substituent on the benzimidazolyl group is selected from H, alkyl, aryl, aralkyl, cycloalkyl or -C(O)N(alkyl)₂), and benzthiazolyl;

Z is selected from the group consisting of -OH and -OC(O)N(alkyl)₂;

10 R³ is hydrogen;
and R⁴ is aryl.

24. The process of Claim 23 wherein



is selected from the group consisting of 1-methyl-benzimidazolyl and benzthiazolyl;
Z is selected from the group consisting of -OH, -OC(O)N(methyl)₂ and -OC(O)N(i-propyl)₂;
R³ is hydrogen;
and R⁴ is phenyl.

20

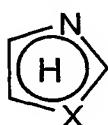
25. The process of Claim 9 wherein



is selected from the group consisting of 1-substituted imidazolyl (where the substituent on the imidazolyl group is selected from H, alkyl, aryl, aralkyl, cycloalkyl or $-C(O)N(alkyl)_2$) and thiazolyl;

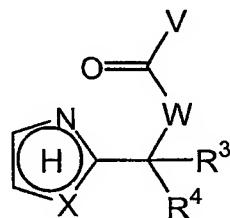
- 5 R⁵ is selected from the group consisting of aryl, alkyl, aralkyl and cycloalkyl;
and R⁶ is selected from the group consisting of $-C(O)N(alkyl)_2$.

26. The process of Claim 25 wherein



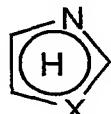
- 10 R⁵ is phenyl;
and R⁶ is $-C(O)N(i\text{-}propyl)_2$.

27. A process for preparing a compound of general formula (Ic):



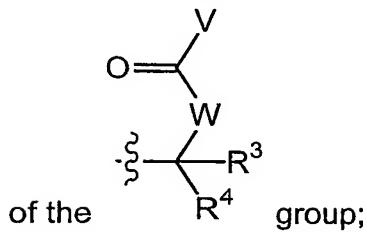
(Ic)

- 15 wherein
X is selected from the group consisting of NH, NR^A and S;



represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group consisting of N, O and S;

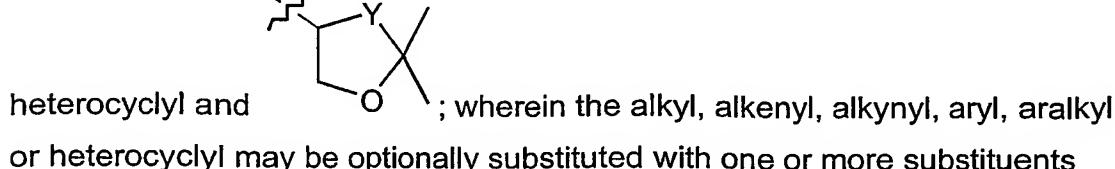
provided that the additional heteroatoms are not at the attachment point



provided that the 5 membered ring remains aromatic in nature;

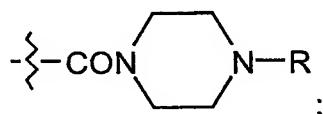
wherein the 5 membered ring is optionally substituted with one to three

- 5 substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, alkenyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the
- 10 cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
W is selected from the group consisting of -O, -NSO₂R, -NSOR, -NCOR, -NCOOR, -NCONR^CR^D, -NOCOR and -NR;
- 15 V is selected from the group consisting of t-butyl, adamantlyl, -N(alkyl)₂, -N(aryl)₂, 2,6,-dimethylphenyl, 2,6-disubstituted phenyl (wherein the substituents are selected from halogen, alkyl or alkoxy), -O-t-butyl, -O-I-propyl and -O-adamantlyl;
- 20 R³ is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aralkyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono- or di-substituted amino, cyano or nitro;
- 25 R⁴ is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, -COOR, -COR, -CONR^CR^D, -alkyl-COOR,



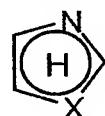
independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono-or di-substituted amino, cyano or nitro; and where Y is selected from the group consisting of O, S and NR^A;

- where R is selected from the group consisting of alkyl, aryl, aralkyl,
 5 cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
 where R^A and R^B are independently selected from the group consisting
 10 of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



- where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
 15 or are joined together to form a 4 to 8 membered heterocyclil ring structure;

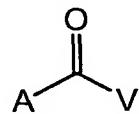
which method comprises reacting a compound of formula (III)



(III)

20

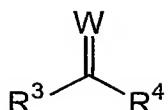
with a compound of formula (IV)



(IV)

wherein A is selected from F, Cl, Br or -OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent;

- 25 and then reacting with a compound of formula (V)

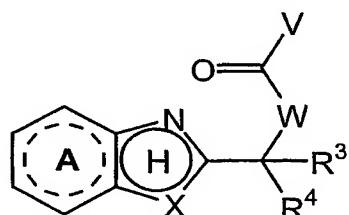


(V)

wherein W is selected from the group consisting of O, NSO₂R, -NSOR, -NCOR, -NCOOR, -NCOR^CR^D, -NOCOR and NR to form the corresponding compound of formula (Ic).

5

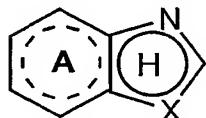
28. A process for preparing a compound of the general formula (Iic)



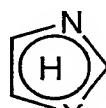
(Iic)

wherein

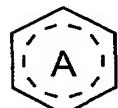
X is selected from the group consisting of NH, NR^A and S;



10 represents a 9 membered ring structure, wherein the five



membered portion of the ring structure - - is aromatic and the six



membered portion of the ring structure - - is saturated, partially unsaturated, or aromatic;

wherein the 5 membered portion of the ring structure is optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono- or di-substituted amino, cyano, nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the

- cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; wherein the 6-membered portion of the ring structure may further 5 optionally containing one to four additional heteroatoms selected from the group consisting of N, O and S;
- wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl, 10 alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent independently selected from halogen, hydroxy, alkyl, 15 halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; W is selected from the group consisting of -O, -NSO₂R, -NSOR, -NCOR, -NCOOR, -NCONR^CR^D, -NOCOR and -NR;
- V is selected from the group consisting of t-butyl, adamantlyl, -N(alkyl)₂, -N(aryl)₂, 2,6,-dimethylphenyl, 2,6-disubstituted phenyl (wherein the substituents 20 are selected from halogen, alkyl or alkoxy), -O-t-butyl, -O-l-propyl and -O-adamantlyl;
- R³ is selected from the group consisting of hydrogen, alkyl, aralkyl, cycloalkyl, fluorinated alkyl, -COR, -COOR and -CONR^CR^D; wherein the aryl, aralkyl or heterocyclyl may be optionally substituted with one or more 25 substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;
- R⁴ is selected from the group consisting of, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl, alkenyl, alkynyl, -COR, -COOR, -CONR^CR^D, -alkyl-COOR,
- (Y)
- heterocyclyl and ; wherein the alkyl, alkenyl, alkynyl, aryl, aralkyl 30 or heterocyclyl may be optionally substituted with one or more substituents

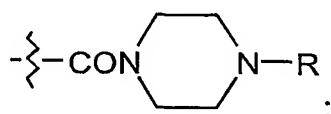
independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, aryl, amino, mono-or di-substituted amino, cyano or nitro; and where Y is selected from the group consisting of O, S and NR^A;

where R is selected from the group consisting of alkyl, aryl, aralkyl,

- 5 cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

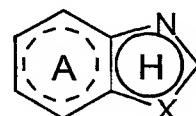
where R^A and R^B are independently selected from the group consisting

- 10 of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



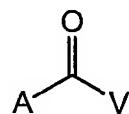
- where R^C and R^D are independently selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocycl ring structure;

which method comprises reacting a compound of formula (VII)



(VII)

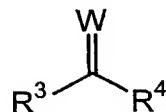
20 with a compound of formula (IV)



(IV)

wherein A is selected from F, Cl, Br or OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent;

- 25 and then reacting with a compound of formula (V)

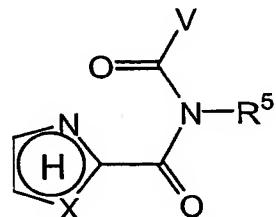


(V)

wherein W is selected from the group consisting of O, NSO₂R, -NSOR, -NCOR, -NCOOR, -NCOR^CR^D, -NOCOR and NR, to form the corresponding compound of formula (IIC).

5

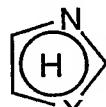
29. A method for preparing compounds of the formula (Id)



(Id)

wherein

X is selected from the group consisting of NH, NR^A and S;



10 represents a 5 membered aromatic ring structure; optionally containing one to two additional heteroatoms selected from the group consisting of N, O and S;

provided that the additional heteroatoms are not at the attachment point of the -C(O)NR⁵R⁶ group;

15 provided that the 5 membered ring remains aromatic in nature;

wherein the 5 membered ring is optionally substituted with one to three substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, alkenyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclil, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -

20 COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclil may be further optionally substituted with one or

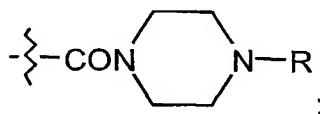
more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

- V is selected from the group consisting of t-butyl, adamantyl, -N(alkyl)₂, -N(aryl)₂, 2,6-dimethylphenyl, 2,6-disubstituted phenyl (wherein the substituents are selected from halogen, alkyl or alkoxy), -O-t-butyl, -O-i-propyl and -O-adamantyl;

- R⁵ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycl; wherein the aryl, aralkyl or heterocycl may be optionally substituted with one or more substituents
- 10 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

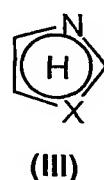
- where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more
- 15 substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

where R^A and R^B are independently selected from the group consisting of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and

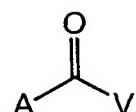


- 20 where R^C is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to
- 25 form a 4 to 8 membered heterocycl ring structure;

which method comprises reacting a compound of formula (III)



with a compound of formula (IV)



(IV)

wherein A is selected from F, Cl, Br or OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent;

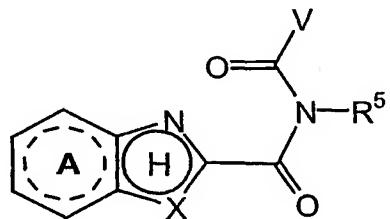
- 5 and then reacting with a compound of formula (VIII)



(VIII)

wherein R⁵ is as previously defined, to yield the compound of formula (Id).

30. A method for preparing compounds of the formula (IId)

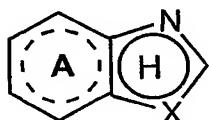


(IId)

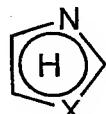
10

wherein

X is selected from the group consisting of NH, NR^A and S;



represents a 9 membered ring structure, wherein the five



membered portion of the ring structure - - is aromatic and the six



- is saturated, partially

- 15 membered portion of the ring structure - - unsaturated, or aromatic;

wherein the 5 membered portion of the ring structure is optionally substituted with one to two substituents independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano, nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent is independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

5 wherein the 6-membered portion of the ring structure may further optionally containing one to four additional heteroatoms selected from the group consisting of N, O and S;

10 wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

15 20 wherein the 6-membered portion of the ring structure may further be optionally substituted with one to four substituents independently selected from the group consisting of halogen, hydroxy, alkyl, halogenated alkyl, cycloalkyl, alkoxy, aryl, aralkyl, heterocyclyl, amino, mono-or di-substituted amino, cyano , nitro, -COOR, -COR, -SO₂R and -CONR^BR^C; wherein the amine substituents are independently selected from alkyl, cycloalkyl, aryl or aralkyl; wherein the cycloalkyl, aryl or heterocyclyl may be further optionally substituted with one or more substituent independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

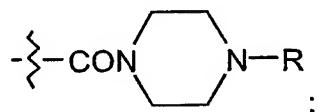
25 V is selected from the group consisting of t-butyl, adamantyl, -N(alkyl)₂, -N(aryl)₂, 2,6,-dimethylphenyl, 2,6-disubstituted phenyl (wherein the substituents are selected from halogen, alkyl or alkoxy), -O-t-butyl, -O-i-propyl and -O-adamantyl;

30 R⁵ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocyclyl; wherein the aryl, aralkyl or heterocyclyl may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

 where R is selected from the group consisting of alkyl, aryl, aralkyl, cycloalkyl, adamantyl, norbornyl, fluorinated alkyl and heterocycle; wherein the

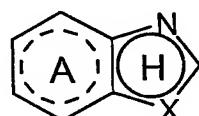
aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro;

where R^A and R^B are independently selected from the group consisting
5 of hydrogen, -R, -COOR, -COR, -SO₂R, -SOR and -CONR^CR^D and



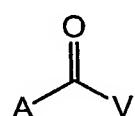
where R^C is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, fluorinated alkyl and heterocycle; wherein the aryl, aralkyl or heterocycle may be optionally substituted with one or more substituents
10 independently selected from halogen, hydroxy, alkyl, halogenated alkyl, alkoxy, amino, mono-or di-substituted amino, cyano or nitro; or are joined together to form a 4 to 8 membered heterocyclyl ring structure;

which method comprises reacting a compound of formula (VII)



(VII)

15 with a compound of formula (IV)



(IV)

wherein A is selected from F, Cl, Br or OC(O)-t-butyl, and wherein V is a sterically hindered group, in a non-protic solvent;

20 and then reacting with a compound of formula (VIII)



(VIII)

wherein R^5 is as previously defined, to yield the compound of formula (IId).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 December 2001 (13.12.2001)

PCT

(10) International Publication Number
WO 01/094318 A3

- (51) International Patent Classification⁷: C07D 233/54, 277/24, 249/08, 233/90
- (21) International Application Number: PCT/US01/16727
- (22) International Filing Date: 22 May 2001 (22.05.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/209,252 5 June 2000 (05.06.2000) US
- (71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, New Brunswick, NJ 08869-0602 (US).
- (72) Inventor: HLASTA, Dennis; 5008 Davis Dr., Doylestown, PA 18901 (US).
- (74) Agent: KENTOFFIO, Joseph, S.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933-7003 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

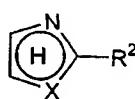
— with international search report

(88) Date of publication of the international search report:
18 July 2002

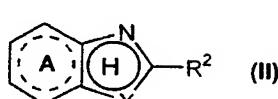
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/094318 A3

(54) Title: METHOD FOR SYNTHESIS OF SUBSTITUTED AZOLE LIBRARIES



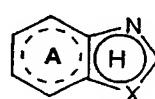
(I)



(II)



(a)



(b)

(57) Abstract: The invention relates to methods of synthesizing libraries of diverse and complex 2-substituted azole compounds of general formula (I) or (II) wherein X, R² and the ring components (a) and (b) are as described herein, novel intermediates useful for synthesizing such substituted azole compounds and methods for identifying and isolating the compounds.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/16727

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D233/54 C07D277/24 C07D249/08 C07D233/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 816 310 A (ELI LILLY AND COMPANY) 7 January 1998 (1998-01-07) claims ----	1
A	WO 00 25768 A (TREGA BIOSCIENCES, INC.) 11 May 2000 (2000-05-11) claims -----	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

7 February 2002

Date of mailing of the international search report

14/02/2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/16727

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		SG	70013 A1		25-01-2000
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WO 0025768	A 11-05-2000	AU	1455500 A		22-05-2000
		EP	1126833 A2		29-08-2001
		WO	0025768 A1		11-05-2000
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